**Novack TA, Banos JH, et al. Impact of Early Administration of Sertraline on Depressive Symptoms in the First Year after Traumatic Brain Injury. J Neurotrauma 2009;26:1921-8.**

Design; Randomized clinical trial

Population/sample size/setting:

- 99 post-TBI inpatients (72 men, 27 women, mean age 35) treated in a university physical medicine/rehabilitation department in Alabama
- Eligibility criteria were age 19-75, referral within 8 weeks of injury, and injury sufficient to require hospitalization; TBI was defined as admission GCS less than or equal to 12 or neuroimaging consistent with trauma (contusion, subdural hematoma)
  Exclusion criteria were pre-existing neurological diagnoses, use of any antidepressant in the hospital or prior to the injury, ongoing steroid treatment, depression necessitating treatment at the time of enrollment, alcohol/drug abuse, or any systemic illness affecting outcome (e.g., renal, cardiac)

Main outcome measures:

- Both groups were treated for 3 months and randomized to sertraline (n=49) or placebo (n=50)
- Sertraline was given at a fixed daily dose of 50 mg for the duration of the study; any patient who was discharged from inpatient care during the study was given sufficient study medication to last until the end of the 3 month trial
- Participants who continued to be treated as inpatients were interviewed weekly for symptoms of depression using the Hamilton Depression Rating Scale (HDRS); those who had been discharged were interviewed by telephone every other week using the same HDRS for symptoms of depression and for adherence to treatment
- If at any interview the HDRS score exceeded 8 points, the participant was interviewed with the Structured Clinical Interview for Depression (SCID-I) to establish a DSM diagnosis of depression; if depression was confirmed the blind was broken for the treating physician but not for the interviewer performing the outcome assessments
- HDRS continued to be administered after the end of the 3 month treatment period; each participant received monthly phone calls from the study nurse, and participants were asked to return to the hospital at 3, 6, and 12 months for a brief clinic visit which included the HDRS and a family interview
- A total of 763 HDRS screenings were done; 10 patients scored 8 or higher and were diagnosed with depression after interview with the SCID-I; thus, the number of new cases of depression during the study was only 10
- Of the 10 cases of depression, 3 were in the sertraline group and 7 were in the placebo group (p=0.19)
- None of the 3 cases of depression in the sertraline group were diagnosed during the 3 month intervention period

- A post-hoc analysis was done based on a cutoff score of 6 or more on the HDRS as evidence of depression; this analysis showed a total of 15 cases of depression, 4 in the sertraline group and 11 in the placebo group (p=0.55)
    - No case of the post-hoc definition of depression occurred in the sertraline group during the 3 month intervention period, but 5 cases occurred in the placebo group (p=0.023)

Authors' conclusions:

- The overall low rate of depression precludes firm conclusions, but the results do not strongly support the idea that early administration of an SSRI confers enduring benefit
- Generalized use of SSRI for the prevention of depression after acute TBI care is not strongly indicated
- The dropout rate (19 in the sertraline group and 10 in the placebo group) was frustratingly high, but not unique to this study
- The low dose of sertraline may not have been sufficient to impact serotonin levels or to affect the emergence of depression
- It is difficult to justify administering a higher dose of sertraline in a prophylactic study which does not offer criteria by which dose increases can be justified

Comments:

- The authors acknowledge most of the difficulties with the study: a small sample size, a low percentage of participants meeting the definition of depression, and the high attrition rate
- The post-hoc analyses cannot be seen as conclusive
- A very large preventive effect of sertraline does appear to be unlikely
- The term "double-blind" is ambiguous; the patients were blinded, as were the treating physicians and the outcome assessors; since these represent three distinct sources of assessment bias, they need to be specified separately

Assessment: Inadequate for evidence about the effect of sertraline in the setting of moderate to severe TBI for the prevention of depression (inconclusive results)